REMARKS

By this Amendment, Claims 1, 6, 7, 8, 10, 12 and 23 are amended. Claims 45-48 are added. Claim 20 is cancelled. Claims 1, 3-19, 21-35 and 45-49 are pending in this Application. Support for the amendments can be found in the Specification and claims as filed, e.g., paragraphs 3-10, 370 and Table 2, and especially at pages 32-44 of the Specification wherein definitions for several of the terms used in the claims are provided. No issue of new matter arises. Applicants respectfully request reconsideration and withdrawal of the rejections set forth in the October 17, 2005 Office Action and allowance of all pending claims.

Rejections under 35 U.S.C. §112, second paragraph

Claims 1 and 3-35 were rejected under 112, second paragraph as allegedly being indefinite. The Office Action includes several numbered paragraphs setting forth these rejections. Applicants respectfully traverse these rejections in corresponding numbered paragraphs.

1. The term "hyperproliferative" was alleged to be unclear. Applicants respectfully refer to paragraph 122 of the application as published wherein "hyperproliferative disorder" is defined as:

> A "hyperproliferative disorder" refers to a disease condition characterized by rapid, or uncontrolled cell division. Hyperproliferative disorders include neoplastic diseases and non-neoplastic diseases.

Claim 3 does not recite "hyperproliferative" in the abstract, but as part of the defined phrase. While Applicants believe that the phrase is used in accordance with its ordinary and customary meaning (See, e.g., MPEP §2111.01. II.), Applicants respectfully assert the right of Applicants to be their own lexicographer. Reconsideration and withdrawal of this rejection are respectfully requested.

2. The rejection objected to the association of asthma and "hyperproliferative". Applicants have amended claim 12 to obviate this rejection. Although the amendment is believed to obviate this rejection, Applicants note that asthma can include a chronic phase wherein smooth muscle proliferation is part of the disease process. Thus amended claim 12 is believed to obviate this rejection, but Applicants believe that the issue of indefiniteness in this context was not properly raised. Reconsideration and withdrawal of this rejection are respectfully requested.

3. The Office Action objected to the association of "allograft rejection" with "hyperproliferative disorder" and "autoimmune disease". With respect to "hyperproliferative disorder", Applicants respectfully submit that claim 12 as amended obviates the rejection. With respect to "autoimmune disease", Applicants respectfully traverse this rejection. Applicants

respectfully submit that considering allograft rejection as a form of autoimmune disease is perfectly reasonable. Once grafted, the allograft becomes part of the new "self". An immune attack launched on oneself is properly considered an autoimmune response. Such autoimmune response or disease is a constant danger facing transplant recipients. These transplanted organs are essential parts of the individual self as were the organs replaced. Remediation of disease is desired. Reconsideration and withdrawal of this rejection are respectfully requested.

4. The Office Action objected to the inclusion of claims 16 and 20 as being allegedly indefinite relating to claim differentiation. Claim 20 is cancelled thereby obviating this rejection. Reconsideration and withdrawal of this rejection are respectfully requested.

5. Claim 12 was rejected in relation to the phrase "hyperproliferative disorder". Applicants respectfully submit that claim 12 as amended above obviates this rejection. Reconsideration and withdrawal of this rejection are respectfully requested.

6. Claim 22 was alleged to be indefinite in reference to the term "CDK". Applicants respectfully traverse this rejection. Applicants respectfully refer to the specification, especially paragraphs 3 and 4 (as published) wherein CDKs are discussed. This class of polymers has developed an understanding in the art. Although new CDKs have been identified since the earlier known CDKs, the class remains well defined and inclusive of additional entries as their characteristics and/or functionalities become known. Indeed a plurality of CDKs exists, hence the numerical designation to differentiate different species of the class. The discovery of additional cyclin dependent kinases in no way hinders understanding of the claim scope. Those of skill in the art can easily identify a polypeptide as a member or not a member of the class of CDKs. Reconsideration and withdrawal of this rejection are respectfully requested.

7. The use of CDK in reference to the complexes recited in claim 23 was objected to. Claim 23 is amended to recite complexes. Reconsideration and withdrawal of this rejection are respectfully requested.

8. With respect to claim 23 the Office Action pointed out three species of cyclin D. These species are also discussed in the specification, for example at paragraph 21. The claim is not amended currently, but if the Examiner maintains a belief that clarity would be improved by reciting that the cyclin D is selected from the group consisting of D1, D2 and D3, Applicants will incorporate the subject matter of new claim 47 into claim 23.

9. Page 5 was referenced with respect to the phrase: "substituted by a nitrogen atom." Suggested substitutions are nitro and amino. Applicants respectfully traverse this rejection.

Apparently, there was a misunderstanding of meanings of "by" and "with". In the listing of claims above, claim 1 is used as an example. At page 3, third line of text the phrase, "substituted by a nitrogen atom" appears. The next line of the claim includes the phrase, "substituted with an X substituent". In the first instance the plain meaning is clear in part because of the preference of nitrogen for three bonds. Note that in aromatics carbons have three bonds as part of the ring structure. A nitrogen atom can easily replace these carbon atoms. That is the carbon can be substituted by a nitrogen atom. On the other hand, the X does not replace the carbon, but is to be incorporated as a substituent on the carbon atom which remains part of the molecule. With this clarification Applicants respectfully submit that there the skilled artisan would see no issue of indefiniteness. Reconsideration and withdrawal of this rejection are respectfully requested.

10. In a rejection similar to that raised in 9 above, the Office action objected to X as =O. Applicants respectfully traverse this rejection. The explanation of this phenomenon relies on equilibrium chemistry. In the case where X is an –OH molecules in solution will not maintain the hydroxyl group as 100% hydroxyl. Depending on solute conditions, a percentage of the hydroxyls will be found in a form where an aromatic double bond has migrated to the oxygen and a hydrogen has bound to a neighboring carbon atom to compensate for the lost aromatic bond. This isomerization occurs spontaneously and reversibly so that an equilibrium situation exists. Isomerization is well known in the art and as such no issue of indefiniteness is implicated. Reconsideration and withdrawal of this rejection are respectfully requested.

11. The Office Action objected to the use of "alkyl" in a generic sense to include hydrocarbons with double or triple bonds. Applicants respectfully submit that indeed formal proper use of the term is restricted to the saturated molecule. Accordingly claim 1 is amended above to recite the more proper "alkylene" term as a generic term to encompass saturated and unsaturated compounds. No issue of new matter arises; the term "alkyl" having been described as being "saturated or unsaturated". Reconsideration and withdrawal of this rejection are respectfully requested.

12. "Heterocyclic" (with respect to "NR5") was alleged to be indefinite. *In re Wiggins* is cited as basis for this rejection. Applicants respectfully submit that *Wiggins* cannot properly be read to hold that "heterocyclic" is *per se* indefinite. Rather, specific recitations and disclosures of the application at hand must be considered in the examination whenever the term is used. In the present claim 1, R4 and R5 are recited as optionally combining to form a heterocyclic ring with the nitrogen atom of NR4R5. A nitrogen atom is known and cannot be interpreted as indefinite as recited herein. R4 and R5 are likewise given meaning in claim recitations. When combining to form the heterocyclic ring, the meaning of R4 and or R5 is further limited because

of constraints placed on the combination. Thus as used in claim 1 "heterocyclic" is defined and *Wiggins* cannot be said to generically apply. Reconsideration and withdrawal of this rejection are respectfully requested.

13. The Office Action suggested that NR6 as an unsubstituted nitrogen renders the claim indefinite. Claim 1 is amended above to delete the phrase at issue. Reconsideration and withdrawal of this rejection are respectfully requested.

14. The Office Action objected to the phrase "mixed type of neoplasm" as possibly indicating more than "mixed neoplasm". Applicants respectfully submit that the expression is understood within the art, especially in view of the examples set forth in the specification. As evidence, Applicants reference USP 5,109,024 that uses the expression "mixed types of neoplasias" in a similar context. The term in the context of compounds for treating neoplasms is clearly understood by the skilled artisan. An alternative as expressed in the Office Action in paragraph 16. below might be "mixed cellularity neoplasia" that is used in reference to many of the examples set forth in the specification, especially Hodgkin's lymphoma. Paragraph 16. apparently objects to this expression in the present context. Thus, Applicants respectfully submit that the best expression in the present context is the wording used in the specification and further embellished by examples in the specification. In view of this clarification, reconsideration and withdrawal of this rejection are respectfully requested.

15. Applicants believe that the response in 14 above suffices to traverse the issues raised in paragraph 15 of the Office Action. Reconsideration and withdrawal of this rejection are respectfully requested.

16. The association of "mixed type of neoplasm" or "mixed neoplasm" or "Mixed cellularity Hodgkin's lymphoma" with Hodgkin's disease was discussed. Applicants view this understanding as an extension of issues raised in paragraphs 14 and 15 above. Comments above are believed responsive to issues raised herein thereby obviating this aspect of the rejection. Reconsideration and withdrawal of this rejection are respectfully requested.

17. The term "alkyl" in reference to unsaturated hydrocarbons was deemed unclear. Applicants have amended claim 1 as suggested by the Examiner. Reconsideration and withdrawal of this rejection are respectfully requested.

18. The Office Action objected to the association of the expression "alkyl group" where no carbon atom is present. Claim 1 is amended to obviate this rejection. Reconsideration and withdrawal of this rejection are respectfully requested.

19. The Office Action objected to the misspelling of "cervix". The misspelling is corrected in the set of amended claims above. Reconsideration and withdrawal of this rejection are respectfully requested.

20. The Office Action queried how claim 10 further limits claim 5. Claim 10 is amended above for clarity. Claim 10 specifically recites the neoplastic disease as melanoma whereas claim 5 recites a larger Markush group. Reconsideration and withdrawal of this rejection are respectfully requested.

21. The Office Action queried about the antecedent basis for "phenyl". Claim 1 is amended to move the paragraph at issue to be more clearly subordinate to the recitation of the "phenyl" recitation that serves as the antecedent basis. Reconsideration and withdrawal of this rejection are respectfully requested.

22. A typographic error was noted in claim 20. Claim 20 is cancelled. Reconsideration and withdrawal of this rejection are respectfully requested.

23. The Office Action alleged that claim 1 was indefinite in its inclusion of circular definitions. Claim 1 is amended above to obviate this rejection. Specifically, claim 1 is amended so that descriptions of R_4 and R_5 no longer recite themselves as self-substituents. Reconsideration and withdrawal of this rejection are respectfully requested.

Rejection under 35 U.S.C. §112, first paragraph

Beginning at page 6, the Office Action rejected claims 3-22 and 24-26 as allegedly lacking enablement. *Wands* factors were discussed as part of the analysis. Claims 1, 23 and 27-35 are not included in this rejection.

The breadth of claims is noted to include possibly billions of compounds. Claim 1, though not a party to this rejection is amended above to, for instance no longer recite the infinite compounds possible with, e.g., R_4 serving as its own substituent *ad infinitum*. The scope of diseases was characterized as "colossal". Breadth of a claim is not sufficient grounds for rejection. The instant invention relates to compounds that bind CDKs thus interfering with mitosis. Since mitosis is ubiquitous in cell biology (Cells do not replicate without mitosis.), the scope of effect of the compounds is likewise ubiquitous. Cells that undergo undesired mitosis such as those listed in the Office Action are valid targets for treatment with compounds of the present invention. For example, abnormal tissue growth resulting from cell proliferation requires that the cells cycle through the metabolic pathway including completing mitosis. Arresting or

inhibiting mitosis is a valuable tool for treating such diseases. Cancer is one such hyperproliferative disease. No matter which part of the body is affected by cancerous cells, these cells require mitosis for proliferation. For example, no matter the etiology of the disease, such as leukemia, the cells of the disease must undergo mitosis for the disease to progress. Blocking mitosis according to the instant invention is thus a benefit for treating these diseases. Similar issues obtain when discussing carcinomas, sarcomas and/or melanomas regardless of location.

Regarding autoimmune diseases, the Office Action listed several dozen. While specific autoimmune disease symptoms are dependent on the target of the immune system and the cells types mediating the immune response, even antibodies, a humoral or non-cellular component of the immune system arise from cells (B cells or B lymphocytes). Cellular components of the immune system, such as T cells, macrophages and NK cells do not act individually, but are required in great numbers to mount an immune attack. Rheumatoid arthritis as well as other autoimmune diseases has an angiogenesis component. Many autoimmune diseases have a smooth muscle proliferation component. Interfering with immune cell proliferation is one tool for ameliorating symptoms of autoimmune disease. The Office Action alleged that for a compound or genus to be effective against autoimmune diseases generally "is contrary to medical science." Applicants beg to differ citing glucocorticoids as a counter example.

Regarding apoptosis, Applicants agree that apoptosis is a natural process, but also note that if unchecked, i.e., allowing every cell to apoptose, death of the organism is the logical conclusion. The point is that biologic processes are in balance. Cells and organisms expend energy to prevent themselves from reaching equilibrium conditions. In certain instances known in the art, apoptosis is initiated in cells at a particular point in the cell cycle. Preventing cells from cycling through mitosis can prevent or reduce apoptosis. Similarly arresting cell cycle at a specific stage may increase the likelihood of initiating apoptosis in response to a natural or unnatural agent. Thus compounds of the present invention used in conjunction with other agents are expected to be extraordinarily effective.

Part I. (page 15) of the Office Action discussed protection from antineoplastic agents. This rejection is an enablement rejection, not specifically alleging indefiniteness. Antineoplastic agents may target dividing cells. The instant invention, featuring compounds and methods that arrest mitotic cell division can thereby protect cells from these agents. One of ordinary skill in the art is cognizant of these matters and would have had no difficult understanding in which situations to beneficially apply the present invention.

In part J. the Office Action implied two issues for rejection. On the one hand, CDKs were recognized as useful, in fact, essential enzymes in lifeforms. Secondly, the Office Action observed that multiple CDKs were known. Although multiple CDKs are known, they all belong to the same class of compounds and each CDK has a binding site for ATP, the binding site targeted by compounds of the instant invention. Applicants agree that CDKs are useful enzymes. But as alluded above, life is a balancing act whereby an organism uses metabolism to maintain a non-equilibrium balance. Disease occurs when the balance deviates from what is desired. Treatment of disease involves providing outside influence to help the body restore or approach a desired state. Thus, while in some cases complete inhibition, e.g., to treat an infective agent, may be desired, in other cases, treatment titrates activities within the organism to restore, approach or maintain a desired balance. Thus inhibiting CDKs does have utility. Those of ordinary skill in the medical arts recognize the need to use proper dosage to achieve the desired balance. Moreover, the various CDKs are well known in the art. The ordinarily skilled artisan is quite capable without undue experimentation of applying the present invention to one or more of the CDKs.

Restinosis (claim 13) generally refers to renarrowing of a coronary artery after angioplasty or stenting. While the definition has been more broadly applied, the thickening of the arterial wall in a coronary artery serves as an illustrative example. The arterial wall thickening is due to cell, e.g., smooth muscle cell, proliferation. Inhibiting the proliferation short term especially during the immediate healing phase is beneficial for survival of the individual. Autoimmune disease such as rheumatoid arthritis includes an angiogenesis component, i.e., a hyperproliferative phase. Thus the compounds and methods of the present invention are applicable to this disease. Even with autoimmune diseases that are not well-controlled, the present invention is useful in controlling growth during the healing phase. The compounds of the present invention through stasis action on cell growth or proliferation thus can be beneficially applied to prevent or decrease restinosis and other proliferative disease.

The Office Action made a blanket assertion that physiological activity is "generally considered to be an unpredictable factor". Once again Applicants beg to differ. Physiology is a branch of science following application of the scientific method. Hypotheses are proposed and tested. Valid results that can be repeated may confirm hypotheses or lead to additional hypotheses. The science would not be considered a science if it were indeed unpredictable. As a clear example, lack of food and water will cause death in a predictable fashion following physiologic principles. Thus physiological activity is not *per se* unpredictable. In the present circumstance, predictable interaction of a CDK with a compound of the present invention

interferes with cell cycling. The results of many such binding interactions are predictable. With respect to the present invention, the binding interaction is predictable. The general comment regarding physiology thus does not apply in the present circumstance.

Direction or guidance was discussed at page 15 at part (3). Applicants respectfully mention that in the medical arts, dosage determination is very routine, in fact required for government approval. Thus determining dosage is routine and does not require undue experimentation.

At part (4) the Office Action asserted that inhibition of three CDKs "cannot be said to be representative of the class as a whole." Applicants respectfully submit that CDKs are so named because they are each members of the class of cyclin dependent kinases. As members of the class they are expected to share similarities. The site of interaction between the compounds of the present invention and each CDK is the ATP binding site of the CDK. Hydrolysis of ATP by the bound CDK is thus prevented, arresting CDK activity. Thus, there is a presumption that in the absence of contrary data, members of the class would behave similarly.

At page 16, paragraph I. the Office Action observes that although compounds are known to treat a range of cancers, not all cancers have been treated by a single compound. Applicants respectfully agree that inoperative treatments exist in the art of cancer treatment. For example, a chemotherapeutic agent or cocktail may often be beneficial to a patient only for a limited or more preferably for an extended period of time. Patients continue to die while undergoing treatment. Treatment may still be considered beneficial even in the absence of complete elimination or remission of disease. Several cancers are refractory to virtually all treatment. For example some cancers rapidly adapt to chemical agents, other cancers may require dosages that elicit undesired side effects, thus limiting treatment or effectiveness of treatment. These phenomena are known in the art. Although the present invention is applicable in general to hyperproliferative disease, using cancers for example as a point of discussion, CDK activity is altered in a way that the compounds preferably inhibit proliferation with a therapeutic window that is satisfactory for anti-tumor therapy but allows the patient to regain full health. This preferable outcome, as noted in the Office Action is rare, but less preferable outcomes are still beneficial and achievable. Depending on the cancer, the stage of cancer and the state of the patient, dosage is set to balance effect on desired proliferation with undesired proliferation. While not perfect in every respect, such treatment is beneficial and routine in the art. The present invention provides additional tools for controlling this balance. Compounds of the present invention may be used in combination with other anti-tumor agents to improve anti-tumor efficacy. For normal cells (neurons, smooth muscle, others that we mention), there are disorders where slowing their proliferation/cell cycle will have a protective effect (anti-apototic for neurons during stroke) or

limit unwanted proliferation (restinosis, angiogenesis, others). Experimentation, not undue, is typical in the art of cancer treatment. Since in this art the experimentation is routine, and not undue, this issue cannot be said to render the claims "not enabled".

The Office Action breaks out four categories of autoimmune diseases: Antibody mediated, Immune complex mediated, Antibody and T cell mediated, and complement deficiency mediated. The first three each involve antibodies and immune cascades mediated by the initial antibody binding. Preventing or minimizing activation and proliferation of B cells responsible for the autoimmune antibodies would be expected to ameliorate symptoms of associated autoimmune diseases. As for complement deficiency mediated autoimmune diseases where hyperproliferation is involved, the skilled artisan would have recognized these embodiments as a class of non-working embodiments with no experimentation whatsoever. Thus undue experimentation is not implicated.

At page 20, part III., the Office Action specifically addresses claim 14, p21, for example, is known to be involved in immune system function, modulating T-cell proliferation by interacting with a CDK binding site separate from the ATP binding site of the present inventive compounds. Treatment of all immune diseases that are T-cell dependent thus may benefit from the instant invention. Atherosclerosis and asthma each are known to involve smooth muscle proliferation. Proliferative disorders are known to be involved in diabetic nephropathy. Thus modulating proliferation can benefit patients afflicted by these diseases.

The Office Action mentions that sarcomas are generally treated with surgery. Surgery is often used in conjunction with other modes of treatment, including chemotherapeutic agents. The present invention provides compounds and treatments for controlling undesired proliferation of cells. Modulated proliferation may be used in conjunction with surgery and/or other therapies. The novelty of the present therapeutic approach is supported by the Office Action. Other compounds that attempt to attack tumors by different means would be expected to possibly have vastly different results. The Office Action failed to cite any compounds of the class instantly claimed. Thus the weak response to chemotherapy using other agents is irrelevant to the compounds and methods instantly claimed. Reconsideration and withdrawal of this rejection are respectfully requested.

Double Patenting Rejection

Applicants appreciate the Examiner's notification of the possible double patenting issue. A terminal disclaimer is being prepared for immediate filing should compound claims of the present application be found otherwise allowable.

Conclusion

In view of the above amendments and remarks, Applicants respectfully submit that the application is now in condition for allowance and request prompt indication of such. Should the Examiner wish to suggest additional amendments that might put the application in even better condition for allowance, the Examiner is requested to contact the undersigned at the telephone number listed below. Applicants are prepared to file a Terminal Disclaimer to effect immediate issuance of a Notice of Allowance if the Examiner indicates allowability of claims to which such Disclaimer would apply.

Respectfully submitted,

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